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Diffusion tensor imaging fiber tractography for evaluating diffuse axonal injury

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Abstract

Patients with Diffuse axonal injury (DAI) frequently exhibit cognitive disorders chronically. Radiologic recognition of DAI can help understand the clinical syndrome and to make treatment decisions. However, CT and conventional MRI are often normal or demonstrate lesions that are poorly related to the cognitive disorders. Recently, diffusion tensor imaging (DTI) fiber tractography has been shown to be useful in detecting various types of white matter damage. The aim of this study was to evaluate the feasibility of using DTI fiber tractography to detect lesions in DAI patients, and to correlate the DAI lesions with the cognitive disorders. We investigated two patients with chronic DAI. Both had impaired intelligence, as well as attention and memory disorders that restricted their activities of daily living. In both patients, DTI fiber tractography revealed interruption of the white matter fibers in the corpus collosum and the fornix, while no lesions were found on conventional MRI. The interruption of the fornix which involves the circuit of Papez potentially correlates with the memory disorder. Therefore, DTI fiber tractography may be a useful technique for the evaluation of DAI patients with cognitive disorders.

Keywords: *Diffuse axonal injury, cognitive disorder, diffusion tensor imaging fiber tractography, corpus callosum, fornix, circuit of Papez*

Introduction

Diffuse axonal injury (DAI) is identified as one of the most important causes of cognitive disorders in patients with traumatic brain injury (TBI). DAI results from damage to the white matter caused by unequal rotation and/or deceleration/acceleration forces on the brain parenchyma, which stretch and injure the axons [1–3]. DAI lesions tend to be multiple and small. The common sites are at the grey/white matter interface, the corpus callosum, the basal ganglia, the internal capsule, the hippocampus, the dorsolateral aspect of the brain stem, and the cerebellum [1, 4, 5].

Currently, no technique is accurate for diagnosing and assessing the distribution of DAI. CT and conventional MRI are known to underestimate the true extent of DAI and correlate poorly with cognitive disorders [6]. Consequently, there is considerable interest in developing more sensitive diagnostic tools. Diffusion tensor imaging (DTI) has been reported to be useful in detecting white matter damage, which may not be prominent on T1-weighted and T2-weighted MR imaging [7]. Recently, brain fiber tracking using DTI data has been applied to visualize the white matter tract of the brain [8–11]. Fiber tracking can be created, based on

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similarities between neighbouring voxels in the shape and orientation of the diffusion ellipsoid, and can be used for analysis of axonal networks in the brain [9–11]. This new technique was also used to investigate large white matter bundles in the vicinity of brain lesions, for example, the pyramidal tract of the motor system [9–11]. There are a few reports of DTI fiber tractography for DAI [2–4, 12], and its correlation with cognitive disorders remains unclear. Accordingly, we evaluated qualitatively DTI fiber tractography in patients with DAI, and examined the relationship of the imaging evaluation with their cognitive disorders.

Methods

Subjects

We studied 3 healthy volunteers (a 27-year-old woman, 29-year-old woman, and a 36-year-old man) who had no history of closed head trauma, and 2 patients (a 26-year-old-man and a 34-year-old man) who suffered traumatic brain injury and have had clinical findings compatible with DAI. These two patients had achieved good recovery of their motor functions but continued to have cognitive disorders, and consequently had restricted activities of daily living (ADL). We obtained ethics committee approval at our university hospital prior to the study. Informed consent was obtained from the volunteers and patients or from family members before the study.

Neuropsychological tests

Neuropsychological tests were performed to detect the extent of the cognitive disorders for the DAI patients. The Mini-Mental State Examination [13] and Wechsler Adult Intelligence Scale-Revised [14] were performed for the intelligence tests. The Trail-Making Test [15–17] and Paced Auditory Serial Addition Task [18] were performed for the attention tests. The Wechsler Memory Scale-Revised [19] and Rivermead Behavioral Memory Test [20] were performed for the memory function tests. The Wisconsin Card Sorting Test-Keio version [21] and the Behavioral Assessment of the Dysexecutive Syndrome [22] were performed for the executive function tests.

Evaluation of ADL and behavioural problems

ADL and behavioural problems were evaluated by the Functional Independence Measure (FIM) and the Functional Assessment Measure (FIM + FAM). The FAM adds 12 items on cognitive, behavioural, communication, and community function to the FIM. Therefore FIM + FAM has been proposed as a method to extend the range of the FIM, particularly when assessing the functional status in rehabilitation patients with brain injury [23].

MRI acquisition

MRI was performed using a 1.5 tesla imager (Signa Horizon LX CV/i, GE Medical Systems, Milwaukee, WI, USA) with a conventional head coil. The subject's head was fixed in the head coil with a band and cushions to reduce motion artifacts. The MRI included T1-weighted imaging, T2-weighted imaging, T2*-weighted gradient-echo imaging, and diffusion tensor imaging (DTI). The T1-weighted MR imaging was obtained using a spin echo sequence with a repetition time (TR) of 550 ms and an echo time (TE) of 20 ms, and the T2-weighted MR imaging by a fast spin echo sequence with a TR of 4000 ms, a TE of 112 ms and an echo train length of 13. The T2*-weighted gradient-echo MR imaging was obtained with a TR/TE/flip angle of 600 ms/26 ms/30 degree. The DTI was performed by fat suppressed spin-echo type single-shot echo-planer imaging (TR/TE/NEX = 11000/78/2, a 3.5 mm slice thickness without an interslice gap, 96×128 matrix, FOV: 23×23 cm). Motion probing gradients (MPGs) were applied in 17 noncollinear directions ($b = 1000$ s/mm^2). Forty slices were obtained to cover the whole brain. Images without MPG were simultaneously obtained with the corresponding slices. The DTI data were transferred to an off-line windows PC with a Celeron processor (2.2 GHz) and 240 MB of memory and analyzed using the diffusion tensor visualizer (dTV) version 1.5 and VOLUME-ONE software (free software by University of Tokyo Hospital, Tokyo, Japan, available from the following site: http://www.ut-radiology.umin.jp/people/masutani/dTV.htm). At first, fractional anisotropy (FA) map images were calculated using the dTV. The brain fiber tractography was performed next using the following procedure: the seed area was defined as a region of interest drawn around the genu to the splenium through the body of the corpus callosum on the midsagittal reformatted image of the FA map, and around the column of the fornix on the axial reformatted FA map. The target area was not defined. The threshold of fiber-tracking was set at a FA > 0.18.

Results

Case 1

The first patient with clinically suspected DAI was a 26-year-old man who consulted our hospital

6 months after a traffic accident. He suffered from impaired intelligence, and attention and memory disorders based upon a battery of neuropsychological tests (Table I). He also showed decreased initiative and lack of insight. The FIM + FAM showed a relatively good score on the motor items, but a low score on the cognitive items (Table II). Therefore, he needed care and/or monitoring for ADL. No abnormal lesions were found on the T1-weighted and the T2-weighted MR images (Figure 1). Multiple signal hypo-intensities in the frontal lobes bilaterally and the left hippocampus were observed on the T2*-weighted gradient-echo MR images (Figure 1). DTI fiber tractography revealed an interruption of the white matter fibers in the corpus callosum and the fornix compared with the images from a normal volunteer (Figure 1).

Case 2

The second patient with clinically suspected DAI was a 34-year-old man who consulted our hospital 20 years after a traffic accident. In spite of his cognitive disorders, he worked very hard and went to college, and finally graduated from the law faculty. However, his cognitive disorders made it difficult for him to find a job. He suffered from impaired intelligence, as well as attention, and memory disorders based upon the neuropsychological tests (Table I). He had good FIM + FAM scores on the motor items, but low scores on the cognitive items (Table II). Therefore, he needed monitoring for his ADL. No abnormal lesions were found on the T1-weighted and the T2-weighted MR images (Figure 2). A signal hypo-intensity in the right side of the splenium corporis callosi was observed on the T2*-weighted gradient-echo MR images (Figure 2). DTI fiber tractography revealed an interruption of the white matter fibers in the corpus callosum and the fornix compared with the images from the normal volunteers (Figure 2).

Discussion

DAI is one of the most frequent types of primary injury that can be seen in patients with TBI [27]. Cognitive and behavioural disorders are often severe

Table I. Neuropsychological performance in 2 DAI patients (results outside the normal range marked with an asterisk).

Test	Case 1 (26-year-old)	Cut-off Mean (SD)	Case 2 (34-year-old)	Cut-off Mean (SD)
Intelligence				
MMSE	29/30	≥24/30	29/30	≥24/30
WAIS-R				
Verbal IQ	86		85	
Performance IQ	46*		75*	
Full scale IQ	67*		79*	
Attention				
TMT (seconds)				
Part A	49*	[25.03(8.94)][1]	49*	[28.88(9.70)][1]
Part B	77	[59.58(28.7)][1]	98	[70.28(27.79)][1]
PASAT	24/60*	[46.3(9.1)][2]	35/60	[41.2(11.4)][2]
Memory function				
WMS-R indices				
General memory	85		80*	
Verbal memory	80*		90	
Visual memory	104		65*	
Attention/concentration	81*		107	
Delayed recall	90		61*	
RBMT				
Total profile score	19/24*	≥20/24	19/24*	≥20/24
Total screening score	7/12*	≥8/12	7/12*	≥8/12
Executive function				
KWCST				
Categories achieved	6	[4.48(1.43)][3]	6	[4.93(1.55)][3]
Perseverative errors of Nelson	2	[1.72(2.80)][3]	0	[1.57(2.97)][3]
Difficulties of maintaining set	0	[0.81(1.03)][3]	0	[0.73(1.23)][3]
BADS				
Total profile score	22/24		18/24	
Age-adjusted scaled score	118		97	

MMSE, Mini-Mental State Examination; WAIS-R, Wechsler Adult Intelligence Scale-Revised; TMT, Trail-Making Test; PASAT, Paced Auditory Serial Addition Task; WMS-R, Wechsler Memory Scale-Revised; RBMT, Revermead Behavioural Memory Test; KWCST, Wisconsin Card Sorting Test-Keio version; BADS, the Behavioural Assessment of the Dysexecutive Syndrome.
[1]Data from Kennedy KJ [24]. [2]Data from Toyokura et al. [25]. [3]Data from Kado et al. [26].

Table II. FIM + FAM scores in 2 DAI patients.

Motor items	Case 1	Case 2	Cognitive items	Case 1	Case 2
Feeding	6/7	7/7	Comprehension	7/7	7/7
Grooming	7/7	7/7	Expression	7/7	7/7
Bathing	7/7	7/7	Social interaction	5/7	4/7
Dressing upper body	7/7	7/7	Problem solving	4/7	6/7
Dressing lower body	7/7	7/7	Memory	4/7	4/7
Toileting	7/7	7/7	Reading	5/7	5/7
Bladder management	7/7	7/7	Writing	6/7	6/7
Bowel management	7/7	7/7	Speech intelligibility	6/7	6/7
Bed transfer	7/7	7/7	Emotional status	4/7	5/7
Toilet transfer	7/7	7/7	Adjustment to limitations	5/7	5/7
Tub or shower transfer	7/7	7/7	Employability	3/7	4/7
Walking	7/7	7/7	Orientation	6/7	6/7
Stairs	7/7	7/7	Attention	5/7	5/7
Swallowing	7/7	7/7	Safety judgement	4/7	6/7
Car transfer	7/7	7/7			
Community access	2/7	6/7			
Total	106/112	111/112	Total	71/98	76/98

7, complete independence (timely, safely); 6, modified independence (extra time, devices); 5, supervision (cuing, coaxing, prompting); 4, minimal assist (performs 75% or more of task); 3, moderate assist (performs 50–74% of task); 2, maximal assist (performs 25–49% of task); 1, total assist (performs less than 25% of task).

problems with chronic DAI. These disorders interfere with the ability to function independently and reentry into society, so DAI has become an issue of public concern. CT and conventional MRI are known to usually fail to uncover any significant abnormalities, even though DAI patients have cognitive disorders [6, 28]. However, an evaluation of the extent of neural injury is essential for making treatment decisions, for devising a rehabilitation program, and for providing appropriate counseling to patients concerning their cognitive disorders.

CT imaging, T1- and T2-weighted MR imaging occasionally show atrophy of white matter tracts such as corpus callosum, fornix, or internal capsule, and ventricular enlargement on chronic stage [6, 27]. Fluid-attenuated inversion recovery (FLAIR) MR imaging can detect many changes in the brain parenchyma in DAI, for instance non-hemorrhagic foci or vasogenic edema [29]. However these findings do not directly delineate the true extent of traumatic axonal damage.

DAI is accompanied frequently by tissue tear hemorrhages. T2*-weighted gradient-echo MR imaging is known to be highly sensitive for detecting brain hemorrhage. It often appears as small areas of low signal intensity on the T2*-weighted gradient-echo MR imaging due to the magnetic susceptibility effect of hemosiderin even during the chronic stage of TBI. Therefore previous reports have indicated that T2*-weighted gradient-echo MR imaging is a useful tool for the evaluation of DAI [5, 30]. In our cases, a few lesions in the frontal lobe, hippocampus, and corpus callosum were observed, which were correlated with the DAI. However, these small, low signal areas are not specific for hemorrhages and can be caused by calcifications, ferritin, air in the sinuses or mastoid bone, or paramagnetic contrast agents [30]. In addition, these low signals on the T2*-weighted gradient-echo MR imaging do not directly show the interruption of axonal connectivity in DAI, and did not closely correlate with the cognitive disorders in our cases, especially in case 2.

DTI fiber tractography can reveal the three-dimensional white matter fiber connectivity of the human brain. Naganawa et al. [2] published, to our knowledge, the first study using DTI fiber tractography in DAI. They found that there was white matter fiber disruption from the seed area around the corpus callosum in a DAI patient. However, cognitive disorders were not assessed in this patient because he had a low level of consciousness even 4 months after the injury. Le et al. [3] reported a correlation between the interruption of the white matter fibers in the posteroinferior aspect of the splenium and the interhemispheric disconnection symptoms of left hemialexia using DTI fiber tractography in a DAI patient. In our cases, fiber disruption from the seed area around the corpus callosum and the fornix were observed in comparison with normal healthy volunteer images on DTI fiber tractography. These findings are believed to be due to interrupted axonal connectivity in DAI. Our DAI patients exhibited various cognitive disorders, but did not have obvious interhemispheric disconnection symptoms; for instance left hand anomia, left upper limb ideomotor dyspraxia, or left visual field dyslexia in spite of fiber disruption in the corpus callosum. Peru et al. [31] mentioned that interhemispheric disconnection symptoms from partial callosal lesions may be

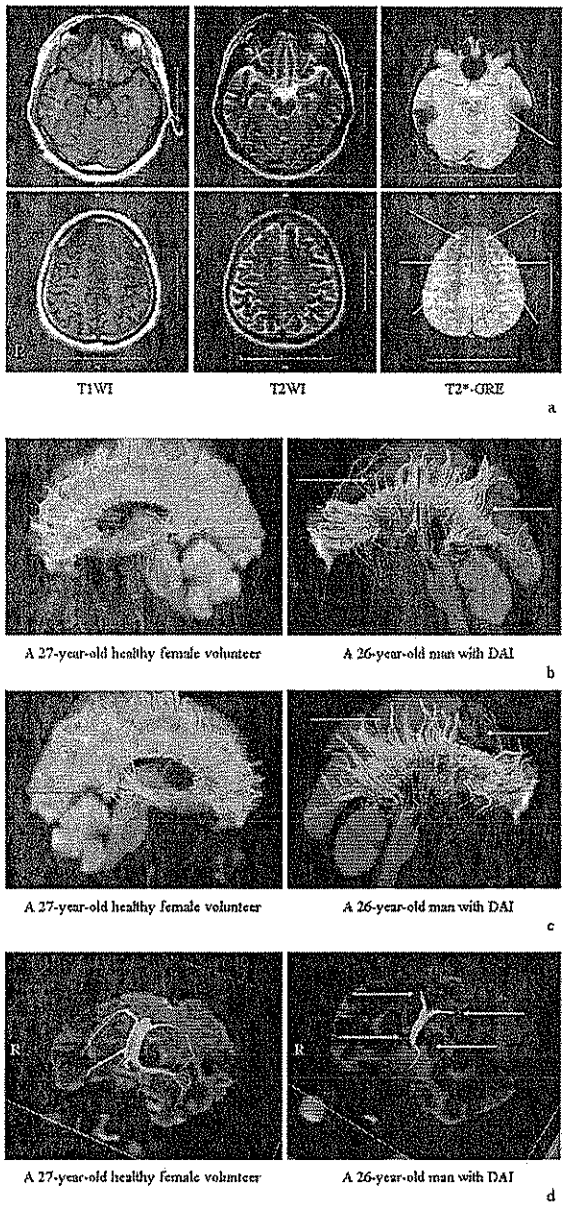

Figure 1. The MRI of a 26-year-old man with DAI. (a) No abnormal lesions were found on the T1-weighted (T1WI) and the T2-weighted (T2WI) MR images. Multiple small foci showing signal hypo-intensity were detected in the left hippocampus and the frontal lobes bilaterally on the T2*-weighted gradient-echo MR images (T2*-GRE) (arrows). (b) DTI fiber tractography from the seed area around the corpus callosum on the left side midsagittal image. There were fewer fibers extending to the frontal, parietal, and occipital white matter and they were even absent in some areas (arrows), in comparison with the normal volunteer image. (c) DTI fiber tractography from the seed area around the corpus callosum on the right side midsagittal image. There were fewer fibers extending to the frontal, parietal, and occipital white matter and they were even absent in some areas (arrows), in comparison with the normal volunteer image. (d) DTI fiber tractography from the seed area around the fornix. The fornix fibers were interrupted (arrows), in comparison with the normal volunteer image.

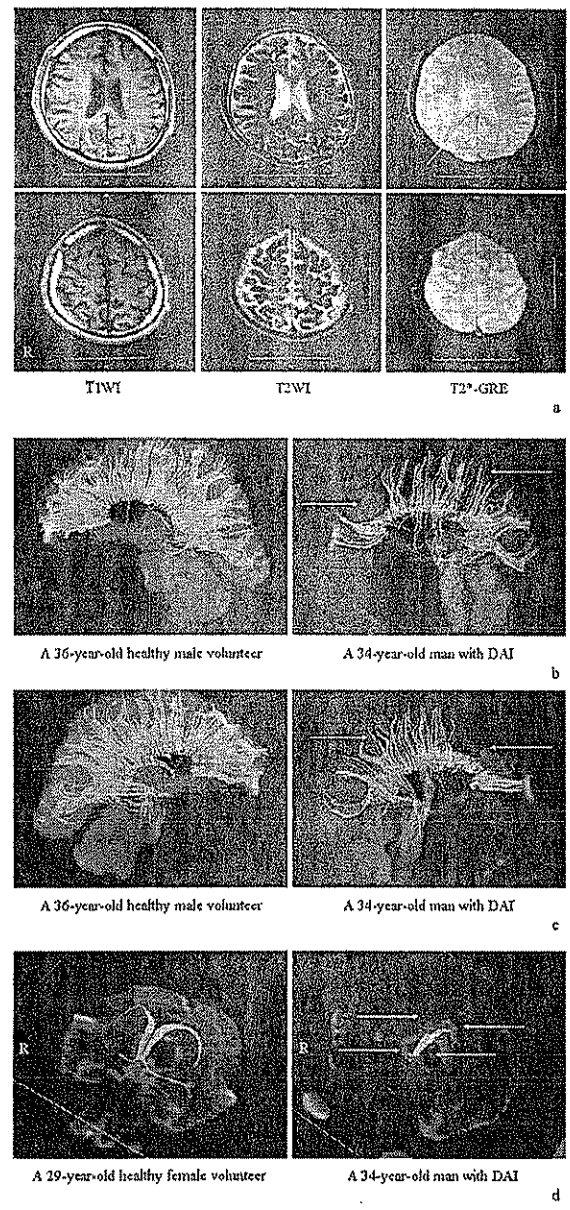

Figure 2. The MRI of a 34-year-old man with DAI. (a) No abnormal lesions were found on the T1-weighted (T1WI) and the T2-weighted (T2WI) MR images. A small focus showing signal hypo-intensity was detected on the right side of the splenium corporis callosi on the T2*-weighted gradient-echo MR images (T2*-GRE) (arrow). (b) DTI fiber tractography from the seed area around the corpus callosum on the left side midsagittal image. There were fewer fibers extending to the frontal, parietal, and occipital white matter and they were even absent in some areas (arrows), in comparison with the normal volunteer image. (c) DTI fiber tractography from the seed area around the corpus callosum on the right side midsagittal image. There were fewer fibers extending to the frontal, parietal, and occipital white matter and they were even absent in some areas (arrows), in comparison with the normal volunteer image. (d) DTI fiber tractography from the seed area around the fornix. The fornix fibers were interrupted (arrows), in comparison with the normal volunteer image.

reversible over time, possibly due to functional compensation by intact contingents of callosal fibers. Our patients also may have had interhemispheric disconnection symptoms at an earlier stage, nearer the time of the trauma, but these symptoms may have improved due to functional compensation by an intact portion of the corpus callosum.

To our knowledge, this is the first report demonstrating an interruption of the fornix fibers on DTI fiber tractography in DAI patients. The fornix fibers are involved in the circuit of Papez. The circuit of Papez is a classical neural circuit representing one of the anatomic substrates of memory function [32, 33]. Consequently, interruption of the fornix fibers potentially correlates with the memory disorder in our DAI patients.

Moreover, our DAI patients suffered from not only a memory disorder but also impaired intelligence, inattention, and low scores of the FIM+FAM on cognitive items. The presence of the various remaining cognitive disorders cannot be explained only by disrupted fibers in the corpus callosum and the fornix on the DTI fiber tractography. However, fiber disruption in the corpus callosum and the fornix may suggest that more diffuse axonal disconnection is present in other areas commonly associated with DAI, for instance at the grey/white matter interface, the deep periventricular white matter, or the hippocampus. It is thought that these axonal disconnections alter the neural network system of the brain, and they might be the cause of the various cognitive disorders.

Conclusion

DTI fiber tractography can directly visualize the lesions of DAI, which can not be reliably detected by conventional methods. Indeed, these findings may be able to provide imaging findings that correlate with the cognitive disorders. Accordingly, this new technique may have the potential to be applied to planning rehabilitation therapy, and predicting the neurologic prognosis in DAI patients. Further studies of DTI fiber tractography, and correlation with the cognitive disorders in a larger number of DAI patients, are needed to confirm these correlations.

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

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GABRIEL STEIF and EVA STEIF,

08 CV 2892 (NRB)

Plaintiffs,

-against-

GREYHOUND LINES, INC. and WILLIAM LEE HENLEY, JR.,

Defendants.

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AFFIDAVIT and EXHIBITS

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To: Attorney(s) for:
Sir(s):

PLEASE TAKE NOTICE that a of which the within is a (true) (certified) copy

[ ] NOTICE OF ENTRY *was duly entered in the within named court on* 2008

[ ] NOTICE OF SETTLEMENT *will be presented for settlement to the Hon. one of the judges of the within named court at the Courthouse at* on , 2008 at o'clock

Dated:

Yours, etc.,
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